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**Review Article**

## Is it Time for the Introduction of Colostomy Free Survival in Rectal Cancer Patients

**Abstract**

The rectum is considered the straight part of the bowel although it's not straight with at least three folds. Sometimes defined as the last 12 cm of the large bowel other consider it as the last 15 cm. Surgeons mark it starting at the anorectal ring, anatomist use the dentate line, more consensus and agreements is needed for the rectum as a structure. Also there is a lot of difference between the upper and lower part of the rectum, anatomically and embryologically. Differences between both can be easily recognized in treatment options, treatment results, and consequences of treatment as regard permanent colostomy and sphincter control. With the growing evidence of the watch and wait policy it may be worthy to start separating the upper rectum from its lower part, which may help to direct us to different treatment approaches and the introduction of colostomy free survival as one of the end treatment results. Hence our suggestion of the separation between the upper and lower rectum.

**Introduction**

The rectum named as the last 15- to 20-cm of the large bowel is still searching for its identity. Anatomists divide it into three parts: upper, middle, and lower rectum. From the anal verge, these three parts can be defined as: the lower rectum 0 to 6 cm, the middle rectum 7 to 11 cm and the upper rectum 12 to 15 cm [1]. There is controversy among surgeons and anatomist in the definition in its start and end. The start defined at the level of S3 by anatomists and at the sacral promontory by surgeons. The distal limit is regarded as the muscular anorectal ring by surgeons and as the dentate line by anatomists [2]. Some surgeons prefer to define its start and end in numbers; e.g. bowel part within 15 cm from the anal verge others may stop it at 12 cm [3]. In clinical trials the rectum is recruited as a single organ, although treatment between the upper and lower part may be totally different; the upper part can easily be treated by anterior resection while the lower part may need ultra-low anterior resection or abdominoperineal resection with its consequence of permanent colostomy. The need for preoperative concurrent chemoradiation for down staging in the lower part may be of extreme importance which may not be the case in the upper rectum. In this review we are trying to highlight the major difference between both upper and lower rectum: embryologically, anatomically, treatment results and even surgical management difference. Which may help in redefinition of the true rectum and the introduction of the concept of colostomy free interval as an important end results, not only disease free or overall survival.

**Embryology and anatomical difference**

During embryological development of the rectum and the urogenital system, the caudal end of hindgut dilates to form the cloaca. The cloaca gives upper half of the anal canal and the lower rectum, while the rest of the rectum arises from the hindgut [3-5]. The lower part derived from the cloaca is surrounded by condensed extra-peritoneal connective tissue [4]. Which is not the case in the upper part. Veins from the upper two-thirds of the rectum are drained by the superior rectal vein; however veins from the lower third of the rectum are drained by the middle and inferior rectal veins into the internal iliac veins. The venous rectal drainage may give the chance for tumours of the lower rectum and anal canal to directly establish pulmonary metastases without hepatic metastases [5,6]. Which may give a privileged method of spread to the lower rectum.

**Screening difference**

There is convincing evidence from many randomised controlled trials (RCTs) [7-9]. As well as a Cochrane library systematic review of those RCTs [10]. that colorectal cancer mortality was reduced with population-based screening using a guaiac-based faecal occult blood test. Screening for the lower rectum is easy, frequency of blood detection as well as digital rectal examination may help to save more lives and this may be an interesting point of research and a separate screening program.

## The mesorectum and the lower rectum

The mesorectum is defined as the adipose tissue with lymphovascular and neural structures encapsulated by a fascia, the so-called mesorectal fascia. The mesorectum is cone-shaped, with the tip starting at the level of the sacral promontory at the origin of the superior rectal artery and ending at the level where the levator ani muscle inserts into the rectal wall, which makes the layer between the muscularis propria and the surrounding perirectal tissues disappear.

High local recurrence rates, ranging from 25% to 50% in the past, have markedly decreased in recent years as a result of the recognition of the circumferential margin (CRM) involvement as one of the main cause of local recurrence which moved the surgeons globally to use the total mesorectal excision approach (TME) as a standard of care, however, site of the tumour has still an impact on the capability of the surgeon to obtain a negative CRM. Local recurrence in a series of 1008 patients was less common (14 %) after resection of tumours of the upper third of the rectum compared with the middle (21 %) ( $P = 0.02$ ) or lower thirds (26 %) ( $P > 0.001$ ). Although this was in the era where total mesorectal excision (TME) was not yet the standard of care [11]. However the presence or absence of tumor within 1mm of the surgical circumferential resection margins (of the excised surgical specimen) strongly influences outcome and is an independent predictor of survival and local recurrence [12,13].

Also, the presence of tumor at the circumferential resection margin seen in Magnetic Resonance imaging (MRI) influences whether the patient should receive preoperative treatment or not [14,15]. Even with neoadjuvant therapy (both radiotherapy and radiochemotherapy) Nagtegaal and Phil Quirke [16]. showed clearly that the predictive value of the CRM for local recurrence is significantly higher than when no preoperative therapy has been given (hazard ratio 6.3 v 2.0, respectively;  $P > 0.05$ ). The Mercury study [17]. showed that 33% of low rectal tumours treated with abdominoperineal excision had circumferential resection margin involvement, compared with 13% of those treated with total mesorectal excision anterior resection. Similar rates were seen in other studies, such as the Leeds [18]. APR excision study (CRM involvement 36.5% for abdominoperineal excision vs 22.3% for AR), the MRC CLASICC [19]. Study (21% for APR excision vs 10% for anterior resection), the Dutch total mesorectal excision study (30.4% for abdominoperineal excision vs 10.7% for anterior resection), and the Norwegian rectal cancer project [20]. (13% for abdominoperineal excision vs 5.5% for anterior resection. Furthermore, involvement of the CRM is a powerful predictor of both development of distant metastases [HR 2.8; (95% CI: 1.9 to 4.3)] and survival [HR 1.7; (95% CI: 1.3 to 2.3)] [21]. All these results show clearly that the height of the tumor is considered as a critical factor for local recurrence. Pahlman et al and others [22–24]. estimated lower recurrence rate in the lower third of the rectum to be in the range of 10%–15% compared to 5%–10% and 2%–5% in the middle and upper rectum respectively. The risk of local recurrence is also related to the position of the tumor within the circumference of the rectum. In the series of Chan et al [25]. the rate of local recurrence was 15% (95% CI: 11–22) for

tumors affecting the anterior side of the rectum but was 5.8% (95% CI: 3–11) for other locations. Clearly the anterior aspect of the TME dissection is more difficult to perform in the narrow lower pelvis. This effect is more pronounced in lower rectal tumors where the mesorectum is very thin, which carries a higher risk of local recurrence than tumors in upper part.

## Sphincter sparing in the preoperative treatment settings

There is still a debate concerning the value of neoadjuvant concurrent chemoradiation (CRT) in sphincter sparing. Five clinical trials included in a Cochran meta-analysis [26]. showed that preoperative CRT alone, versus preoperative RT significantly increased the rate of complete pathological response (OR 2.12–5.84,  $P < 0.00001$ ), however this was not translated into higher sphincter preservation rate (OR 0.92–1.30,  $P = 0.32$ ). This concept was also clear in an elegant systemic overview for ten randomised trials included 4596 patients with rectal cancer, all treated by preoperative chemoradiation. Results failed to show any improvement in the frequency of sphincter preservation [27]. Definitely distance of the tumor from the anal verge play a critical role in the surgical decision of sphincter preservation, starting to divide rectum patients into upper and lower part may help us to define the true value of concurrent chemoradiation in sphincter saving surgeries. Reluctance to cut through a previous tumor site by the surgeons is an old concept as surgeons were not sure about tumour sterilization, as well as a continuous doubt about the type and quality of biopsy that can be taken to confirm PCR [28]. Fitzgerald et al. [29]. in a metaanalysis showed that margin less than 1 cm still confer adequate local tumor control, especially when radiotherapy added to surgery. When neither TME nor radiotherapy was part of the treatment regimen, the data clearly supported margins greater than 1 cm. Bujko et al in a systematic review of the literature identified 17 studies correlated the results of treatment to surgical margins <1 cm (948 patients) versus >1 cm (4626 patients); five studies in relation to a margin of  $\leq 5$  mm (173 patients) versus >5 mm (1277 patients), and five studies showing results in a margin of  $\leq 2$  mm (73 patients), the local recurrence rate was 1.0% higher in the <1-cm margin group compared to the >1-cm margin group (95% CI -0.6 to 2.7;  $P = 0.175$ ). The corresponding figures for  $\leq 5$  mm cutoff point were 1.7% (95% CI -1.9 to 5.3;  $P = 0.375$ ). The pooled local recurrence rate in patients having  $\leq 2$  mm margin was 2.7% (95% CI 0 to 6.4) [30] and they concluded that a margin less than 1 cm in selected patients may not jeopardize safety. This narrow margin may not be essential in the upper rectum, however it's critical in low lying rectal tumors. This concept of narrow margin was obvious in the German rectal cancer trial, which suggested that a change in operative strategy may be safely performed [31]. Out of 462 patients with tumor lying 0–5 cm from the anal verge only 295 patients had abdominoperineal resection, which may give a hope for better outcome. This narrow margin and less APR may be the results of better surgical techniques as shown in Gerard et al [32]. comprehensive review, which showed a clear improvement in sphincter saving procedures since 1995, but, they attributed this improvement, to the improvement in surgical techniques and not a direct effect of the neoadjuvant treatment.

We do believe that the clear benefit from neoadjuvant treatment may not appear except if the lower rectum was treated separately with many different strategies including higher doses of radiation, better chemotherapeutic agents, adoption of the 1mm margin surgery.

### Is it time for rectum saving survival (RSS) and/or colostomy free survival (CFS) as a surrogate end point

Abdominoperineal resection leading to permanent colostomy was previously thought to be the standard of care for all but small anal cancers occurring below the dentate line with approximately 70% of patients surviving 5 or more years [33]. Later on, concurrent chemoradiation became the standard of care without one single randomized trial [33–35]. Complete remission rate approached the 80% a figure that we didn't reach yet in rectal cancer, but colostomy free survival rate at 5-year cumulative incidences of tumor-related colostomy is about 26% after excluding 8% of cases that may be therapy related [36]. In the Habr Gama recently published series [37], for 183 patients treated with concurrent chemoradiation 90 patients were put on stringent watch and wait policy (without immediate surgery), When all procedures in the complete cohort of 90 patients with initial cCR were considered, sphincter preservation was ultimately possible in 77 patients (86%) and organ preservation in 70 patients (78%). Interestingly none of the patients had recurrences exclusively detected by radiologic assessment and this may be an interesting area of research.

Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) [38]. is a recently published propensity-score matched cohort analysis study, gave more highlight and confidence about the safety of the watch and wait policy in patients with rectal cancer entered into pCR, in 129 patients managed by watch and wait 44 (34%) had local regrowth. In the matched analyses (109 patients in each treatment group), no differences in 3-year non-regrowth disease-free survival were noted between watch and wait and surgical resection 88% with watch and wait versus 78% with surgical resection; Similarly, no difference in 3-year overall survival was noted. By contrast, patients managed by watch and wait had significantly better 3-year colostomy-free survival than did those who had surgical resection. Rectum sparing watch and wait approach may be of great concern only in lower rectum, due to the permanent colostomy bag price, much easier to follow and detect early recurrences clinically before any radiological evidence, something that may not be possible in higher level rectal tumours.

Dabirian et al published a comprehensive quality of life study for physical, psychological, nutritional, family and economic aspects patients with colostomy, their study showed that most of the patients may suffer from some irritation, rash around colostomy, sleep disturbance, some degree of family problem, and social difficulties. Others reported initial sexual problems which was resolved later on [39].

Sixty-nine potential studies were identified. Fourteen trials found that people undergoing abdominoperineal excision/Hartmann's operation did not have poorer quality of life measures than patients undergoing anterior resection. The rest

of the studies found some difference, but not always in favour of non-stoma patients. Due to clinical heterogeneity and the fact that all studies were observational trials, meta-analysis of the included studies was not possible [40]. Further prospective trials may answer this question.

### Final suggestions

1. The rectum to be divided into surgical rectum(true rectum) up to 10 cm from the anal verge (4cm anal canal + 6cm true rectum which is accessible by DRE and can be treated by contact therapy), and upper rectum (Anatomical rectum) that end at the rectosigmoid junction. This measurement can be done also using the MRI.
2. New staging system with separate staging of the upper and the lower rectum, in a similar way to the gastroesophageal junction tumors, with inclusion of the CRM as part of staging.
3. Staging to incorporate pathological remission in the lower rectum only.
4. Recruitment of the lower rectum patients separately in clinical trials.
5. Colostomy free/ Rectum Saving survival is another end point to be added for treatment results.
6. The dose of radiation should be at least 60Gy with concurrent chemoradiation in the lower rectum whenever possible.
7. Assessment of response can be done early during treatment as well as 8 weeks after the end of treatment.

### Conclusion

We advocate the consideration of the lower rectum as a separate organ, separated from its outer counterpart, which may help more patients to avoid suffering from the expected side effects from an aggressive surgery that ends up by a "colostomy bag".

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